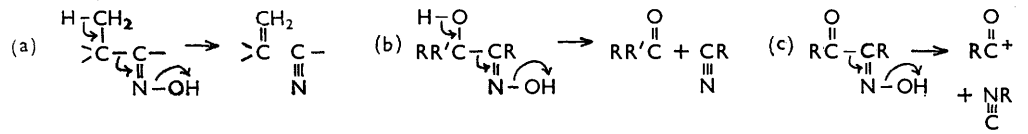
## 703. *Aza-steroids. Part VI.*[1] *Beckmann Rearrangement of Some α-Hydroxy-ketoximes.*

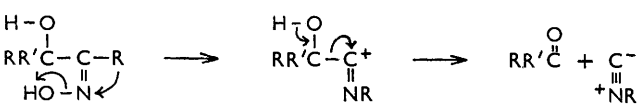
By C. W. Shoppee and S. K. Roy.

5-Hydroxy-5α-cholestan-4- and -6-one oximes, by Beckmann change with thionyl chloride at −20°, give nearly quantitative yields of ω-cyano-5-ketones, which are converted by hydroxide or alkoxide ions into 3-cyano-A-norcholest-3-ene and 6-cyano-B-norcholest-5-ene, respectively.

In the preceding Part[1] we reported that Beckmann rearrangement of five steroid ketoximes (not otherwise substituted) gave the expected lactams which in only two of these cases were accompanied by the abnormal products, ω-cyano-olefins. The formation of ω-cyano-olefins (*a*) appears to parallel the ready production of aldehydes or ketones and cyanides from *anti*-α-hydroxy-oximes * (*b*) and of acylium cations and cyanides from *anti*-α-keto-oximes * (*c*) by " second-type " Beckmann change:[2-4]



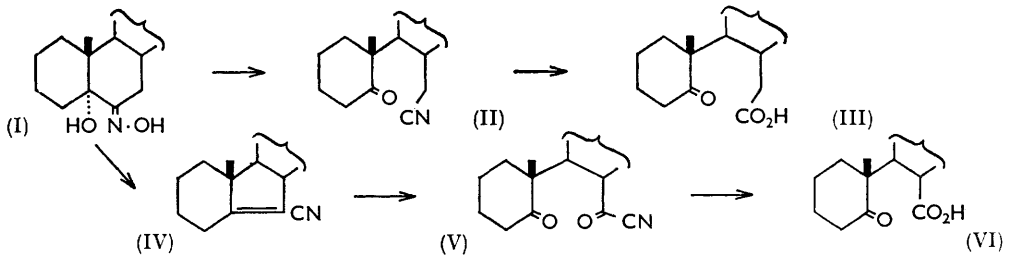
* *syn*-α-Hydroxy-oximes and *syn*-α-ketoximes yield aldehydes, ketones or acylium ions, and isocyanides; the stereoelectronic situation here prohibits concurrent electron transfers and requires consecutive Beckmann rearrangement with *trans*-interchange and " second-type " Beckmann change with cleavage in the resulting cation:



[1] Part V, preceding paper.
[2] Werner and Piguet, *Ber.*, 1904, **37**, 4295; Werner and Detscheff, *Ber.*, 1905, **38**, 69.
[3] Blatt and Barnes, *J. Amer. Chem. Soc.*, 1934, **56**, 1148.
[4] Ferris, *J. Org. Chem.*, 1960, **25**, 12.

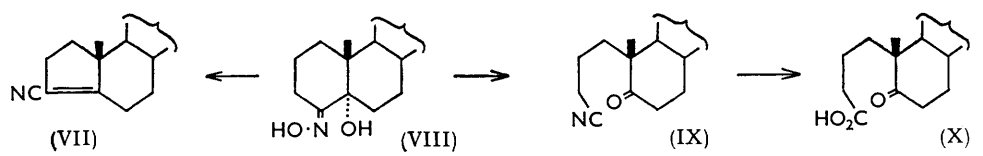
It seemed therefore of interest to examine the behaviour of some steroid α-hydroxy-ketoximes.

5-Hydroxy-5α-cholestan-6-one oxime (I), on treatment with thionyl chloride at −20° or with hydrogen chloride in ether at 15°, gave a nearly quantitative yield of the ω-cyano-ketone (II), $\nu_{max.}$ 2145 (C≡N) and 1706 cm.$^{-1}$ (C=O), hydrolysed by hydrochloric–acetic acid to the known acid [5] (III). The hydroxy-oxime (I) in refluxing methanolic 4N-potassium hydroxide or ethanolic sodium ethoxide gave, probably through the keto-acid (III) by the Claisen reaction, the conjugated cyanide (IV), $\lambda_{max.}$ 227 mμ (log ε 4·1), $\nu_{max.}$ 2210 (C≡N),

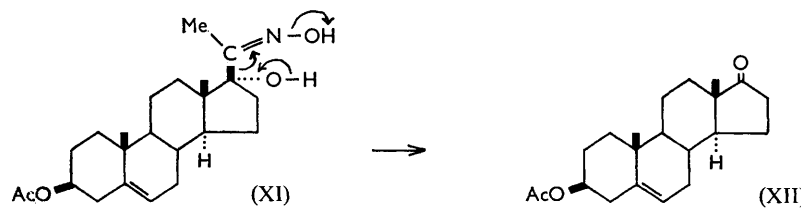



1630 cm.$^{-1}$ (C=C). The infrared spectrum of this product did not show hydrogen deformation frequencies in the 1000—660 cm.$^{-1}$ region, and the ditertiary character of the double bond is consistent with its resistance to hydrogenation and the resistance of the cyano-group to hydrolysis under drastic conditions. The structure 6-cyano-B-norcholest-5-ene (IV) was proved by ozonolysis to the α-keto-cyanide (V), which on alkaline hydrolysis gave the known acid [6] (VI).

5-Hydroxy-5α-cholestan-4-one oxime (VIII), on similar treatment with thionyl chloride or ethereal hydrogen chloride, gave a nearly quantitative yield of the ω-cyano-ketone (IX), hydrolysed by hydrochloric–acetic acid to the known acid [7] (X). The hydroxy-oxime (VIII), on treatment with hydroxide or alkoxide ions, gave the αβ-unsaturated cyanide (VII), $\lambda_{max.}$ 225 mμ (log ε 4·17), $\nu_{max.}$ 2212 (C≡N), 1635 cm.$^{-1}$ (C=C). The double bond therein could not be hydrogenated, and its ditertiary nature is shown by the absence of hydrogen deformation frequencies in the 1000—660 cm.$^{-1}$ region of the infrared spectrum.

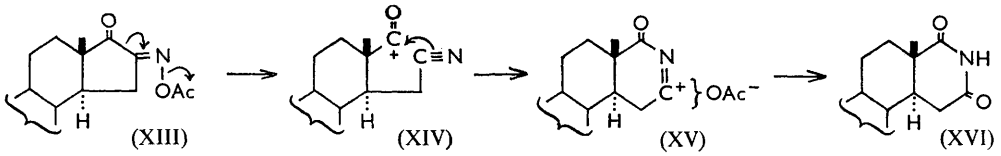



It seems possible that the conversion of 3β-acetoxy-17α-hydroxypregn-5-en-20-one oxime (XIV) by phosphoryl chloride–pyridine at 0° in 98% yield into androstenolone acetate [8] (XII) may proceed by elimination of methyl cyanide rather than by normal rearrangement to the 17β-acetamido-17α-alcohol and loss of acetamide.




[5] Windaus and Resau, *Ber.*, 1914, **47**, 1229; Windaus, *Ber.*, 1920, **53**, 488; Lettré, *Z. physiol. Chem.*, 1933, **218**, 67; Dauben and Fonken, *J. Amer. Chem. Soc.*, 1956, **78**, 4736.
[6] Jacobs and Brownfield, *J. Amer. Chem. Soc.*, 1960, **82**, 4033.
[7] Lettré, *Z. physiol. Chem.*, 1933, **221**, 73.
[8] Schmidt-Thomé, *Annalen*, 1957, **603**, 43.

Finally, the rearrangement of 3β-acetoxy-5α-androstane-16,17-dione 16-oxime acetate (XIII) by acetic anhydride–pyridine at 20° to the enol acetate [9] (XV) clearly takes place by " second-type " Beckmann change to the ω-cyano-acylium ion (XIV), which undergoes cyclisation to give (XV). The structure of the enol acetate (XV) is proved by alkaline hydrolysis to the imide (XVI).




(XIII) (XIV) (XV) (XVI)

## Experimental

For general experimental directions, see *J.*, 1958, 3458 and Part V.[1]

*5-Hydroxy-5α-cholestan-6-one Oxime* (I).—Cholest-5-ene (20 g.) was converted by treatment with peracetic acid and subsequent alkaline hydrolysis into 5α-cholestane-5,6β-diol [10,11] (13 g.), m. p. 120—121°, which was oxidised by *N*-bromosuccinimide to 5-hydroxy-5α-cholestan-6-one [10,11] (8·2 g.), m. p. 150—151°. The hydroxy-ketone (8 g.) was refluxed with hydroxylamine hydrochloride (12 g.) and sodium acetate trihydrate (16 g.) in ethanol for 4 hr., to give the oxime (I), having double m. p. 170°/190—192° after recrystallisation from ethanol [Found (after sublimation at 150°/0·1 mm.): C, 78·0; H, 11·35. $C_{27}H_{47}NO_2$ requires C, 77·7; H, 11·35%].

*Rearrangement of 5-Hydroxy-5α-cholestan-6-one Oxime* (I) *to 6-Cyano-5,6-secocholestan-5-one* (II).—(*a*) The oxime (I) (800 mg.) was treated with thionyl chloride (10 c.c.) at −20° (carbon dioxide–acetone); the colourless solution was at once poured into an excess of 4N-potassium hydroxide at 20°, and the product extracted with ether. Crystallisation was induced by trituration with pentane, and recrystallisation from ethanol gave *5-oxo-5,6-secocholestano-6-nitrile* (II) (700 mg.), m. p. 96—97° [Found (after drying at 40°/0·3 mm. for 16 hr.): C, 81·3; H, 11·45; *N*, 3·45. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35; N, 3·5%].

(*b*) The oxime (I), in ether, was treated with a stream of dry hydrogen chloride at 15° for 0·5 hr.; the solvent was removed in a vacuum and the crystalline residue recrystallised from ethanol, to give the nitrile, m. p. and mixed m. p. 96—97°.

*Hydrolysis of the Nitrile* (II): *5-Oxo-5,6-secocholestan-6-oic Acid* (III).—The cyano-ketone (II) was refluxed with 10N-hydrochloric acid and acetic acid (1 : 1) for 4 hr., to afford, after working up in the usual way, 5-oxo-5,6-secocholestan-6-oic (III) as an oil, $\nu_{max.}$ 1710 cm.$^{-1}$, whose infrared spectrum was identical with that of a genuine specimen prepared [5] from cholest-5-ene.

*6-Cyano-B-norcholest-5-ene* (IV).—The oxime (I) (500 mg.) was refluxed with (*a*) a solution of sodium (3 g.) in ethanol (40 c.c.) for 3 hr. or (*b*) methanolic 4N-potassium hydroxide for 4 hr. The usual isolation procedure gave an oil, which was dissolved in ether and treated with dry hydrogen chloride. The precipitate was filtered off, and the filtrate evaporated to give a brown semi-solid product (300 mg.) which was chromatographed on aluminium oxide (10 g.) in hexane. Elution with benzene gave *6-cyano-B-norcholest-5-ene* (IV) (250 mg.), m. p. 131° (from ethanol) [Found (after drying at 20°/0·1 mm. for 16 hr.): C, 85·1; H, 11·3; N, 3·55. $C_{27}H_{43}N$ requires C, 85·0; H, 11·4; N, 3·6%].

*Ozonolysis of 6-Cyano-B-norcholest-5-ene* (IV): *5-Oxo-5,7-seco-6-norcholestan-7-oic Acid* (VI).—6-Cyano-B-norcholest-5-ene (100 mg.) in chloroform (30 c.c.) was treated with ozonised oxygen at −10° for 2 hr. After removal of chloroform at 30—40°/10 mm., the semi-solid product was refluxed with methanolic 2N-potassium hydroxide (20 c.c.) for 2 hr. After the usual working up, the acid fraction formed an oil which crystallised when moistened with pentane and kept at 0° for a week. Recrystallisation from pentane gave 5-oxo-5,7-seco-6-norcholestan-7-oic acid, m. p. 182°, mixed m. p. 180—182° (lit.,[6] 188°). The infrared spectrum was identical with that of a synthetic specimen prepared by the procedure of Jacobs and Brownfield.[6]

[9] Heard, Ryan, and Balker, *J. Org. Chem.*, 1959, **24**, 172.
[10] Reich, Walker, and Collins, *J. Org. Chem.*, 1951, **16**, 1753.
[11] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.

*5-Hydroxy-5α-cholestan-4-one Oxime* (VIII).—Cholest-4-ene [m. p. 81·5°, lit.,[12] 82—83·5° (purified [12] through the 4β,5α-dibromide, m. p. 117°)] (18 g.) was converted by treatment with peracetic acid and subsequent alkaline hydrolysis into 5α-cholestane-4β,5-diol [11] (10 g.), m. p. 171—172°, which was oxidised with *N*-bromosuccinimide to 5-hydroxy-5α-cholestan-4-one [11] (9·5 g.), m. p. 159°, $[\alpha]_D$ +54° (*c* 0·9). The hydroxy-ketone (8 g.) was refluxed with hydroxylamine hydrochloride (12 g.) and sodium acetate trihydrate (16 g.) in ethanol for 4 hr. to furnish the oxime (VIII), double m. p. 190°/212—214°, after recrystallisation from acetone [Found (after drying at 80°/0·2 mm. for 12 hr.): C, 78·0; H, 11·15. $C_{27}H_{47}NO_2$ requires C, 77·7; H, 11·35%].

*Rearrangement of 5-Hydroxy-5α-cholestan-4-one Oxime* (VIII) *to 5-Oxo-4,5-secocholestano-6-nitrile* (IX).—(*a*) The oxime (320 mg.) was treated with thionyl chloride (5 c.c.) at −20°; the colourless solution was at once poured into an excess of 4N-potassium hydroxide at 20°. The usual extraction procedure gave an oil, which crystallised when moistened with pentane; recrystallisation from ethanol gave the *nitrile* (IX) (300 mg.), m. p. 66—68°, $\nu_{max.}$ 2145, 1706 cm.$^{-1}$ [Found (after drying at 20°/0·3 mm. for 16 hr.): C, 81·0; H, 11·35. $C_{27}H_{45}NO$ requires C, 81·15; H, 11·35%].

(*b*) The oxime, on treatment with dry hydrogen chloride in ether at 15° for 0·5 hr., evaporation of the solution in a vacuum, and recrystallisation of the product from ethanol gave the nitrile (IX), m. p. and mixed m. p. 66—68°.

*5-Oxo-4,5-secocholestan-4-oic Acid* (X).—The cyano-ketone (IX) was refluxed with 10N-hydrochloric acid–acetic acid (1 : 1) to furnish, after the usual working up, 5-oxo-4,5-secocholestan-4-oic acid [7] (X) as an oil, $\nu_{max.}$ 1710 cm.$^{-1}$. The infrared spectrum was identical with that of a genuine specimen prepared by ozonolysis of pure cholest-4-ene, m. p. 81·5°.

*3-Cyano-A-norcholest-3-ene* (VII).—The oxime (VIII) (500 mg.) was refluxed with a solution of sodium (3 g.) in ethanol (40 c.c.) for 3 hr. The product, dissolved in ether, was treated with dry hydrogen chloride; the insoluble base hydrochloride was filtered off, the filtrate evaporated, and the product chromatographed on aluminium oxide (10 g.) in hexane. Elution with benzene gave *3-cyano-A-norcholest-3-ene* (VII) (250 mg.), m. p. 90—92° [Found (after drying at 40°/0·3 mm. for 6 hr.): C, 85·35; H, 11·7. $C_{27}H_{43}N$ requires C, 85·0; H, 11·35%].

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Sydney, N.S.W., Australia. [*Received, December 28th,* 1962.]

[12] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2406.